

## CLAIMS AMENDMENTS

Claims 1-28 (canceled).

Claim 29 (new): An isolated variant of the human growth hormone nucleic acid molecule, *GH1*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1.

Claim 30 (new): An isolated variant of the growth hormone nucleic acid molecule, *GH1*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met.

Claim 31 (new): An isolated nucleic acid molecule according to claim 29, wherein said molecule is either gDNA, cDNA or mRNA.

Claim 32 (new): An isolated nucleic acid molecule according to claim 30, wherein said molecule is either gDNA, cDNA or mRNA.

Claim 33 (new): A transcript of the isolated nucleic acid molecule according to claim 29.

Claim 34 (new): A transcript of the isolated nucleic acid molecule according to claim 30.

Claim 35 (new): A transcript of the isolated nucleic acid molecule according to claim 31.

Claim 36 (new): An isolated polypeptide encoded by the nucleic acid molecule according to claim 29.

Claim 37 (new): An isolated polypeptide encoded by the isolated nucleic acid molecule according to claim 30.

Claim 38 (new): An isolated polypeptide encoded by the isolated nucleic acid molecule according to claim 31.

Claim 39 (new): An isolated polypeptide which is a variant of the growth hormone protein, GH, and which includes the substitution Ile179Met.

Claim 40 (new): A screening method for screening an individual suspected of having dysfunctional GH which screening method comprises the steps of:

- (a) obtaining a test sample comprising a nucleic acid molecule of human *GH1* gene from an individual;
- (b) sequencing said molecule;
- (c) examining said sequence for a +1491C→G substitution; and
- (d) where said substitution exists concluding there is a GH dysfunction.

Claim 41 (new): A screening method according to claim 40 wherein said sequencing step involves PCR techniques.

Claim 42 (new): A screening method for screening an individual suspected of having dysfunctional GH, which screening method comprises the steps of:

- (a) obtaining a test sample comprising a growth hormone, GH, polypeptide from said individual;
- (b) sequencing said polypeptide;
- (c) examining said sequence for a Ile179Met substitution; and
- (d) where said substitution exists concluding there is a GH dysfunction.

Claim 43 (new): A kit suitable for carrying out the screening method according to claim 40, which kit comprises:

- (a) an oligonucleotide having a nucleic acid sequence corresponding to region +1491 of a *GHI* gene which region comprises the substitution +1491C→G; and
- (b) an oligonucleotide having a nucleic acid sequence corresponding to the wild-type sequence in the region specified in (a); and, optionally,
- (c) one or more reagents suitable for carrying out PCR for amplifying desired regions of the patient's DNA.

Claim 44 (new): A kit suitable for carrying out the screening method according to claim 42, which kit comprises:

- (a) an oligonucleotide having a nucleic acid sequence corresponding to region +1491 of a *GHI* gene which region comprises the substitution +1491C→G; and
- (b) an oligonucleotide having a nucleic acid sequence corresponding to the wild-type sequence in the region specified in (a); and, optionally,
- (c) one or more reagents suitable for carrying out PCR for amplifying desired regions of the patient's DNA.

Claim 45 (new): An oligonucleotide suitable for use in the method according to claim 40.

Claim 46 (new): An oligonucleotide suitable for use in the method according to claim 42.

Claim 47 (new): An oligonucleotide suitable for use in the kit according to claim 43.

Claim 48 (new): An oligonucleotide suitable for use in the kit according to claim 44.

Claim 49 (new): An isolated growth hormone polypeptide or protein which contains a Ile179Met substitution and which further provides for differential activation of receptor-mediated cell signalling pathways.

Claim 50 (new): An isolated polypeptide or protein according to claim 49 wherein said polypeptide or protein activates the STAT5 pathway but shows reduced activation or the MAPK pathway.

Claim 51 (new): An isolated polypeptide or protein according to claim 50 wherein said reduction in activity of the MAPK pathway is less than 70% of the activity of the wild-type GH protein.

Claim 52 (new): An isolated polypeptide or protein according to claim 51 wherein said reduced activity is less than 50%.

Claim 53 (new): An isolated polypeptide or protein according to claim 50 wherein said reduced activity is less than 45%.

Claim 54 (new): An isolated growth hormone polypeptide or protein which is characterised by possessing a reduced ability to activate the MAP kinase pathway.

Claim 55 (new): An isolated polypeptide or protein according to claim 54 wherein said MAPK pathway is an ERK pathway.

Claim 56 (new): A screening method for screening an individual suspected of having dysfunctional GH which screening method comprises the steps of:

(a) obtaining a test sample from said individual comprising the individual's endogenous growth hormone;

- (b) examining said growth hormone to determine whether and to what extent it will activate the receptor-mediated MAPK cell signalling pathway; and
- (c) where there is a reduction in MAPK cell signalling, with respect to wild-type GH, concluding there is a GH dysfunction.

Claim 57 (new): An antibody specific for the isolated growth hormone polypeptide or protein according to claim 49.

Claim 58 (new): An antibody specific for the isolated growth hormone polypeptide or protein according to claim 50.

Claim 59 (new): An antibody specific for the isolated growth hormone polypeptide or protein according to claim 51.

Claim 60 (new): An antibody specific for the isolated growth hormone polypeptide or protein according to claim 52.

Claim 61 (new): An antibody specific for the isolated growth hormone polypeptide or protein according to claim 53.

Claim 62 (new): An antibody specific for the isolated growth hormone polypeptide or protein according to claim 54.

Claim 63 (new): An antibody specific for the isolated growth hormone polypeptide or protein according to claim 55.

Claim 64 (new): A pharmaceutical composition comprising a nucleic acid molecule according to claim 29 in association with a pharmaceutically acceptable carrier.

Claim 65 (new): A pharmaceutical composition comprising a nucleic acid molecule according to claim 30 in association with a pharmaceutically acceptable carrier.

Claim 66 (new): A pharmaceutical composition comprising a nucleic acid molecule according to claim 31 in association with a pharmaceutically acceptable carrier.

Claim 67 (new): A pharmaceutical composition comprising a nucleic acid molecule according to claim 32 in association with a pharmaceutically acceptable carrier.

Claim 68 (new): A pharmaceutical composition comprising an isolated polypeptide or protein according to claim 49 in association with a pharmaceutically acceptable carrier.

Claim 69 (new): A pharmaceutical composition comprising an isolated polypeptide or protein according to claim 50 in association with a pharmaceutically acceptable carrier.

Claim 70 (new): A pharmaceutical composition comprising an isolated polypeptide or protein according to claim 51 in association with a pharmaceutically acceptable carrier.

Claim 71 (new): A pharmaceutical composition comprising an isolated polypeptide or protein according to claim 52 in association with a pharmaceutically acceptable carrier.

Claim 72 (new): A pharmaceutical composition comprising an isolated polypeptide or protein according to claim 53 in association with a pharmaceutically acceptable carrier.

Claim 73 (new): A pharmaceutical composition comprising an isolated polypeptide or protein according to claim 54 in association with a pharmaceutically acceptable carrier.

Claim 74 (new): A pharmaceutical composition comprising an isolated polypeptide or protein according to claim 55 in association with a pharmaceutically acceptable carrier.

Claim 75 (new): A vector comprising a nucleic acid molecule according to claim 29.

Claim 76 (new): A vector comprising a nucleic acid molecule according to claim 30.

Claim 77 (new): A vector comprising a nucleic acid molecule according to claim 31.

Claim 78 (new): A vector comprising a nucleic acid molecule according to claim 32.

Claim 79 (new): A host cell comprising a vector according to claim 75.

Claim 80 (new): A host cell comprising a vector according to claim 76.

Claim 81 (new): A host cell comprising a vector according to claim 77.

Claim 82 (new): A host cell comprising a vector according to claim 78.

Claim 83 (new): A process for preparing an isolated polypeptide or protein according to claim 49 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GHI*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 84 (new): A process for preparing an isolated polypeptide or protein according to claim 50 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GH1*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 85 (new): A process for preparing an isolated polypeptide or protein according to claim 51 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GH1*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 86 (new): A process for preparing an isolated polypeptide or protein according to claim 52 which comprises:

- (a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GHI*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1; and
- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 87 (new): A process for preparing an isolated polypeptide or protein according to claim 53 which comprises:

- (a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GHI*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1; and
- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 88 (new): A process for preparing an isolated polypeptide or protein according to claim 54 which comprises:

- (a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GHI*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 89 (new): A process for preparing an isolated polypeptide or protein according to claim 55 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GH1*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 90 (new): A process for preparing an isolated polypeptide or protein according to claim 49 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GH1*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 91 (new): A process for preparing an isolated polypeptide or protein according to claim 50 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule,

*GHI*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 92 (new): A process for preparing an isolated polypeptide or protein according to claim 51 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GHI*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 93 (new): A process for preparing an isolated polypeptide or protein according to claim 52 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GHI*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 94 (new): A process for preparing an isolated polypeptide or protein according to claim 53 which comprises:

- (a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GHI*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met; and
- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 95 (new): A process for preparing an isolated polypeptide or protein according to claim 54 which comprises:

- (a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GHI*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met; and
- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 96 (new): A process for preparing an isolated polypeptide or protein according to claim 55 which comprises:

- (a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GHI*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met; and
- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 97 (new): A process for preparing an isolated polypeptide or protein according to claim 49 which comprises:

- (a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GH1*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1, said nucleic acid molecule being either gDNA, cDNA or mRNA; and
- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 98 (new): A process for preparing an isolated polypeptide or protein according to claim 50 which comprises:

- (a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GH1*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1, said nucleic acid molecule being either gDNA, cDNA or mRNA; and
- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 99 (new): A process for preparing an isolated polypeptide or protein according to claim 51 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GH1*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1, said nucleic acid molecule being either gDNA, cDNA or mRNA; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 100 (new): A process for preparing an isolated polypeptide or protein according to claim 52 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GH1*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1, said nucleic acid molecule being either gDNA, cDNA or mRNA; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 101 (new): A process for preparing an isolated polypeptide or protein according to claim 53 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GH1*, comprising the following substitution: +1491 C→G, wherein 1491

refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1, said nucleic acid molecule being either gDNA, cDNA or mRNA; and

- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 102 (new): A process for preparing an isolated polypeptide or protein according to claim 54 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GHI*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1, said nucleic acid molecule being either gDNA, cDNA or mRNA; and

- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 103 (new): A process for preparing an isolated polypeptide or protein according to claim 55 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the human growth hormone nucleic acid molecule, *GHI*, comprising the following substitution: +1491 C→G, wherein 1491 refers to the position of the nucleotide with respect to this transcription initiation site which is designated 1, said nucleic acid molecule being either gDNA, cDNA or mRNA;

and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 104 (new): A process for preparing an isolated polypeptide or protein according to claim 49 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GH1*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met, said nucleic acid molecule being either gDNA, cDNA or mRNA; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 105 (new): A process for preparing an isolated polypeptide or protein according to claim 50 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GH1*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met, said nucleic acid molecule being either gDNA, cDNA or mRNA; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 106 (new): A process for preparing an isolated polypeptide or protein according to claim 51 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule,

*GHI*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met, said nucleic acid molecule being either gDNA, cDNA or mRNA; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 107 (new): A process for preparing an isolated polypeptide or protein according to claim 52 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GHI*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met, said nucleic acid molecule being either gDNA, cDNA or mRNA; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 108 (new): A process for preparing an isolated polypeptide or protein according to claim 53 which comprises:

(a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GHI*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met, said nucleic acid molecule being either gDNA, cDNA or mRNA; and

(b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 109 (new): A process for preparing an isolated polypeptide or protein according to claim 54 which comprises:

- (a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GH1*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met, said nucleic acid molecule being either gDNA, cDNA or mRNA; and
- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 110 (new): A process for preparing an isolated polypeptide or protein according to claim 55 which comprises:

- (a) culturing a host cell comprising a vector, said vector comprising a nucleic acid molecule which is an isolated variant of the growth hormone nucleic acid molecule, *GH1*, comprising a nucleic acid molecule that encodes a protein, i.e. a GH protein, including the substitution Ile179Met, said nucleic acid molecule being either gDNA, cDNA or mRNA; and
- (b) recovering from the culture medium the polypeptide or protein produced by said cell.

Claim 111 (new): A polypeptide or protein produced by the method according to claim 83.

Claim 112 (new): A polypeptide or protein produced by the method according to claim 84.

Claim 113 (new): A polypeptide or protein produced by the method according to claim 85.

Claim 114 (new): A polypeptide or protein produced by the method according to claim 86.

Claim 115 (new): A polypeptide or protein produced by the method according to claim 87.

Claim 116 (new): A polypeptide or protein produced by the method according to claim 88.

Claim 117 (new): A polypeptide or protein produced by the method according to claim 89.

Claim 118 (new): A polypeptide or protein produced by the method according to claim 90.

Claim 119 (new): A polypeptide or protein produced by the method according to claim 91.

Claim 120 (new): A polypeptide or protein produced by the method according to claim 92.

Claim 121 (new): A polypeptide or protein produced by the method according to claim 93.

Claim 122 (new): A polypeptide or protein produced by the method according to claim 94.

Claim 123 (new): A polypeptide or protein produced by the method according to claim 95.

Claim 124 (new): A polypeptide or protein produced by the method according to claim 96.

Claim 125 (new): A polypeptide or protein produced by the method according to claim 97.

Claim 126 (new): A polypeptide or protein produced by the method according to claim 98.

Claim 127 (new): A polypeptide or protein produced by the method according to claim 99.

Claim 128 (new): A polypeptide or protein produced by the method according to claim 100.

Claim 129 (new): A polypeptide or protein produced by the method according to claim 101.

Claim 130 (new): A polypeptide or protein produced by the method according to claim 102.

Claim 131 (new): A polypeptide or protein produced by the method according to claim 103.

Claim 132 (new): A polypeptide or protein produced by the method according to claim 104.

Claim 133 (new): A polypeptide or protein produced by the method according to claim 105.

Claim 134 (new): A polypeptide or protein produced by the method according to claim 106.

Claim 135 (new): A polypeptide or protein produced by the method according to claim 107.

Claim 136 (new): A polypeptide or protein produced by the method according to claim 108.

Claim 137 (new): A polypeptide or protein produced by the method according to claim 109.

Claim 138 (new): A polypeptide or protein produced by the method according to claim 110.

Claim 139 (new): A transcript of the isolated nucleic acid molecule according to claim 32.

Claim 140 (new): An isolated polypeptide encoded by the isolated nucleic acid molecule according to claim 32.